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Lisa A. Haile, J.D., Ph.D.
GRAY CARY WARE & FREIDENRICH LLP
Suite 1100
4365 Executive Drive
San Diego, CA 92121-2133

EXAMINER	
KIM, YOUNG J	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 09/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/662,003	LEE ET AL.	
	Examiner	Art Unit	
	Young J. Kim	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 July 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-27,31-35,40,43-52 and 55-75* is/are pending in the application.

4a) Of the above claim(s) *51,52,57-65 and 71-75* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-27,31-35,40,43-50,55,56 and 66-70* is/are rejected.

7)☒ Claim(s) *50* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The present Office Action is responsive to the Amendment received on July 5, 2006.

Election/Restrictions

This application contains claims 51, 52, 57-65, and 71-75 drawn to an invention nonelected with traverse in the Election made on November 3, 2005. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Preliminary Remark

Claims 1-24, 28-30, 36-39, 41, 42, 53, and 54 have been canceled.

Claims 51-52, 57-65, and 71-75 are withdrawn from further consideration as being drawn to non-elected inventions.

Claims 25-27, 31-35, 40, 43-50, 55, 56, and 66-70 are under prosecution herein.

Priority

It is **maintained** that the effective filing date of the instant application is determined to be November 10, 1997 (of the parent application serial no. 08/967,089).

Applicants traverse the denial of priority and contend that Applicants are entitled to the priority date back to October 26, 1995, corresponding to U.S. Application Serial No. 08/525,596 (now a U.S. Patent No. 5,827,733).

Applicants contend that for example, U.S. Patent No. 5,994,618 to which the instant application claims priority, is directed to myostatin knock-out transgenic animals, which have increased muscle mass as compared to a subject having a wild-type nucleic acid sequence, wherein

Applicants point to example 8, as well as issued-claims 2 and 5 which provide support for methods for detecting variant myostatin in a sample, whether in one or both alleles.

It is respectfully pointed out that the claims are drawn to a method pertaining to a bovine species, and in particular Belgian Blue and Piedmontese, wherein the method further comprises the detection of specific mutations, that is G1056A substitution in Piedmontese and 937-947, 11base pair mutation in Belgian Blue.

The specification of the referenced patent application does not have any written support for the method of detection pertaining to the specific species of bovine as claimed.

While knock-out transgenic animals are employed and disclosed in the above referenced patent document, the knock-out transgenic is mice (column 28, lines 31-67).

The patent document does disclose that non-human animals of the invention embraces bovine, ovine and avian animals (column 16, lines 32-34). However, the patent document does not contemplate the detection of the specific mutations in the specific bovine species so as to provide proper written support under 35 U.S.C. 112, 1st paragraph.

With Applicants' statement regarding that Applicants were the first to clone the bovine myostatin sequence which is provided in the priority applications as well as deposited in GenBank assession no. AF019620 (page 10, bottom paragraph, Response), the disclosure of the gene does not provide support for a method of detecting for a particular phenotype based on a particular mutations found therein. In addition, the support under 35 U.S.C. 112, 1st paragraph requires that the applications from which priority is claimed must provide written support and not other publications. If such were so, then no references would be applicable under prior art rejection.

For the above reasons, the effective priority is properly determined and is accorded the date of November 10, 1997).

Claim Objections

The objection of claims 34, 35, 43, and 44 for reciting non-elected inventions (SEQ ID Numbers, made in the Office Action mailed on January 31, 2006 is withdrawn in view of the Amendment received on July 5, 2006.

The objection of claim 25 for containing a typographical error in the phrase, "indicative of a increased muscle mass," made in the Office Action mailed on January 31, 2006 is withdrawn in view of the Amendment received on July 5, 2006.

Claim 50 appears to contain a typographical error. It appears that claim 50 should depend from claim 45.

Appropriate correction is suggested.

Specification

The objection to the specification for failing to comply with the Sequence Requirement as set forth in 37 CFR 1.821-1.825, made in the Office Action mailed on January 31, 2006 is withdrawn in view of the Amendment received on July 5, 2006, complying with the requirements.

Claim Rejections - 35 USC § 112

The rejection of claims 25-28, 31-37, 41, 42, and 54-56 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter, made in the Office Action mailed on January 31, 2006 is withdrawn in view of the Amendment received on July 5, 2006.

The rejection of claims 28-30, 41, 42, and 54 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for detecting the presence of a target myostatin variant nucleic acid sequence in a nucleic acid-containing specimen, wherein the specimen is bovine,

said bovine being Belgian Blue or Piedmontese, said specimen having increased muscle mass or having a predisposition for increased muscle mass as compared to said specimen having a wild-type myostatin nucleic acid sequence, said method comprising detecting the presence of the target myostatin variant nucleotide sequence, wherein the target myostatin variant nucleotide sequence is a deletion of nucleotides 937-947 in myostatin gene of Belgian Blue; or wherein the target myostatin variant nucleotide sequence is a G to A substitution at nucleotide position 1056 in myostatin gene of Piedmontese, wherein said variant nucleotide sequence is found in both alleles (homozygous), does not reasonably provide enablement for a method for detecting the presence of a target myostatin variant nucleic acid sequence in a nucleic acid specimen, wherein the specimen is avian, ovine, piscine, baboon, murine, or porcine, wherein the target myostatin variant nucleotide is any variant myostatin sequence, and wherein the variant sequence is found in only one allele (heterozygous), made in the Office Action mailed on January 31, 2006 is withdrawn in view of the Amendment received on July 5, 2006, canceling the rejected claims.

The rejection of claims 25-42 and 54-56 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, made in the Office Action mailed on January 31, 2006 is withdrawn in view of the Amendment received on July 5, 2006.

Rejections, New Grounds – Necessitated by Amendment

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 66-70 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 66 recites the phrase, "detecting the presence of Belgian Blue myostatin variant nucleotide sequence having a deletion of nucleotides 937-947."

The claim does not require that the bovine subject be Belgian Blue, but rather that the Belgian Blue myostatin variant nucleotide sequence be detected from the genus of bovine species.

Hence, it becomes indefinite exactly what mutation is being detected since the deletion of 937-947 found on Belgian Blue myostatin gene would not correspond to the same position of other bovine species.

Claims 67-70 are indefinite by way of their dependency on claim 66.

Rejection, Maintained

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 25-27, 31-40, 55, and 56 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for detecting the presence of a target myostatin variant nucleic acid sequence in a nucleic acid-containing specimen, wherein the specimen is bovine, said bovine being Belgian Blue or Piedmontese, said specimen having increased muscle mass or having a predisposition for increased muscle mass as compared to said specimen having a wild-type myostatin nucleic acid sequence, said method comprising detecting the presence of the target myostatin variant nucleotide sequence, wherein the target myostatin variant nucleotide sequence is a deletion of nucleotides 937-947 in myostatin gene of Belgian Blue; or wherein the target myostatin variant nucleotide sequence is a G to A substitution at nucleotide position 1056 in myostatin gene of Piedmontese, wherein said variant nucleotide sequence is found in both alleles

(homozygous), does not reasonably provide enablement for a method for detecting the presence of a target myostatin variant nucleic acid sequence in a nucleic acid specimen, wherein the specimen is avian, ovine, piscine, baboon, murine, or porcine, wherein the target myostatin variant nucleotide is any variant myostatin sequence, and wherein the variant sequence is found in only one allele (heterozygous), made in the Office Action mailed on January 31, 2006 is maintained for the reasons of record.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicants' arguments presented in the Amendment received on July 5, 2006 have been fully considered but they are not found persuasive for the reasons set forth in the, "Response to Arguments" section.

The Rejection:

Factors to be considered in determining whether a disclosure would require undue experimentation are summarized in In Re Wands (858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)). They include (A) the quantity of experimentation necessary, (B) the amount of direction or guidance presented, (C) the presence or absence of working examples, (D) the nature of the invention, (E) the state of the prior art, (F) the relative skill of those in the art, (G) the predictability or unpredictability of the art, and (H) the breadth of the claims.

Breadth of the Claims:

The breadth of the claims embrace a method of detecting the presence of any variant nucleic acid sequence (homozygous/heterozygous, insertion, deletion, polymorphism, substitution) in a

myostatin gene of any non-human subject, wherein the presence of the detection correlates with an increased muscle mass or predisposition for increased muscle mass in said subject.

Whether the application as filed entitles the Applicants for the breadth of the claims covering the above, without requiring of a skilled artisan undue experimentation, is the subject of the present rejection.

Nature of the Invention:

The nature of the invention relates to a method of detecting/diagnosing for a particular mutation (or sequence variance) in a subject, which is correlated with a particular phenotype, in the present case, an increased muscle mass in said subject. As it is well known and established in the art, a particular mutation found in a specific species producing a particular phenotype, cannot, without exception, be assumed to be the same in other species.

Amount of direction/guidance & presence of working examples:

The instant specification discusses the implication of myostatin in muscle development (page 4, lines 23-25). The specification discloses that the individual muscles in myostatin null mice weighs 2 to 3 fold more than its wild-type (page 2, lines 17-19).

The specification, in describing their invention, discloses that the deletion of nucleotides 937-947 in the third exon of the myostatin gene, is found in nucleic acid isolated from Belgian Blue cattle (page 5, lines 3-4), wherein the deletion is responsible for producing a frame-shift that results in a truncated protein (page 5, lines 5-6).

The specification also discloses that the substitution of the nucleotide G to the nucleotide A in exon 3 (page 2, lines 10-11), more particularly, at nucleotide position 1056 (Figure 1C and page 31, lines 10-11) in Piedmontese.

The specification discloses that the above two mutations are found in subjects (Belgian Blue and Peidmontese) which exhibit increased muscle mass while not present in subjects which exhibit non-doubled muscle mass (page 33, line 25-28 and page 34, lines 6-10).

The specification also discloses that the two mutations were homozygous mutations (i.e., present in both alleles; see page 34, lines 4-5 and lines 13-15).

While the specification contemplates that there is a high degree of sequence conservation of myostatin across species (page 33, lines 1-2), the instant specification only shows working examples drawn to the above mutations for specific species of genus, bovine. No other myostatin variance sequences from other species which are correlated with increased muscle mass are disclosed.

The State of prior art & Unpredictability:

McPherron et al. (PNAS, November 1997, vol. 94, pages 12457-12461) evidences that a mutation present in one species responsible for a particular phenotype is not necessarily found in other species of the same genus. McPherron et al. demonstrates that a mutation found in a bovine species, Belgian Blue exhibiting increased muscle mass phenotype is not found in the bovine species, Piedmontese exhibiting the same phenotype. Similarly, the mutation responsible for increased muscle mass phenotype in Piedmontese is not present in Belgian Blue.

Hence, it is clear that correlation of a genotype to a particular phenotype is highly unpredictable and requires empirical determination for each of the species. While a region of myostatin gene might be highly conserved across species, not all mutations are conserved across species. McPherron et al. clearly evidences this fact in that two species of the same genus (bovine) exhibiting a same phenotype (increased muscle mass) comprises mutually exclusive mutation in myostatin gene.

Skill Level:

The skill level of the artisan is deemed high.

Amount of Experimentation:

One of skilled in the art, in order to practice the full scope of the invention would need to first identify mutations which are present in all non-human species, and particularly for avian, ovine, piscine, baboon, murine, porcine, and turkey, the mutations of which are responsible for producing increased muscle mass in each of the species. As the instant specification does not give any guidance to species other than that of the bovine, one of skill in the art must conduct empirical experimentation of each of the species, the experimentation of which must consider a reasonable number of samples so as to produce a statistically significant result, the experimentation of which considers both homozygous and heterozygous mutations, amounting to an undue amount of experimentation to practice the invention commensurate in scope of the claims.

Response to Arguments:

Applicants state that the independent claim 25 has been amended to detecting the presence of a variant Piedmontese myostatin having a homozygous G1056A substitution (page 12, bottom paragraph), and thus the rejection should be withdrawn.

Examiner respectfully points out that the method is still drawn to that which detects for myostatin variant nucleic acid in the subgenus of bovine species. While claim 25 has been amended to recite the phrase, "method comprising detecting the presence of a target Piedmontese myostatin variant nucleotide sequence having a homozygous G1056A substitution," the method is not limited to Piedmontese, that is to say, that the method is open to detecting the G1056A substitution in other bovine species, which was deemed non-enabling in the above rejection of record.

Amending the claim to recite the phrase, "wherein the specimen is from Piedmontese" would overcome this rejection.

Applicants are advised that an after-final amendment to this embodiment would be entered, as following the suggestion of the examiner and further, reducing the issues for appeal.

Rejections, New Grounds – Necessitated by Amendment

Claims 66-70 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for detecting the presence of a target myostatin variant nucleic acid sequence in a nucleic acid-containing specimen wherein the specimen is Belgian Blue and wherein the variant myostatin nucleotide sequence has a deletion of nucleotides 937-947 in the 3rd exon, does not reasonably provide enablement for the method for detecting the presence of a target myostatin variant nucleic acid sequence in a nucleic acid-containing specimen, wherein the specimen is bovine, wherein the variant myostatin nucleotide sequence has a deletion of nucleotides 937-947 in the 3rd exon. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation are summarized in In Re Wands (858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)). They include (A) the quantity of experimentation necessary, (B) the amount of direction or guidance presented, (C) the presence or absence of working examples, (D) the nature of the invention, (E) the state of the prior art, (F) the relative skill of those in the art, (G) the predictability or unpredictability of the art, and (H) the breadth of the claims.

Breadth of the Claims:

The breadth of the claims embrace a method of detecting the presence of 937-947 deletion from a myostatin gene of subgenus of bovine species, wherein the presence of the deletion correlates with an increased muscle mass or predisposition for increased muscle mass said bovine species.

Whether the application as filed entitles the Applicants for the breadth of the claims covering the above, without requiring of a skilled artisan undue experimentation, is the subject of the present rejection.

Nature of the Invention:

The nature of the invention relates to a method of detecting/diagnosing for a particular mutation (or sequence variance) in a subject, which is correlated with a particular phenotype, in the present case, an increased muscle mass in said subject. As it is well known and established in the art, a particular mutation found in a specific species producing a particular phenotype, cannot, without exception, be assumed to be the same in other species.

Amount of direction/guidance & presence of working examples:

The instant specification discusses the implication of myostatin in muscle development (page 4, lines 23-25). The specification discloses that the individual muscles in myostatin null mice weighs 2 to 3 fold more than its wild-type (page 2, lines 17-19).

The specification, in describing their invention, discloses that the deletion of nucleotides 937-947 in the third exon of the myostatin gene, is found in nucleic acid isolated from Belgian Blue cattle (page 5, lines 3-4), wherein the deletion is responsible for producing a frame-shift that results in a truncated protein (page 5, lines 5-6).

The specification also discloses that the substitution of the nucleotide G to the nucleotide A in exon 3 (page 2, lines 10-11), more particularly, at nucleotide position 1056 (Figure 1C and page 31, lines 10-11) in Piedmontese.

The specification discloses that the above two mutations are found in subjects (Belgian Blue and Peidmontese) which exhibit increased muscle mass while not present in subjects which exhibit non-doubled muscle mass (page 33, line 25-28 and page 34, lines 6-10).

The specification also discloses that the two mutations were homozygous mutations (i.e., present in both alleles; see page 34, lines 4-5 and lines 13-15).

While the specification contemplates that there is a high degree of sequence conservation of myostatin across species (page 33, lines 1-2), the instant specification only shows working examples drawn to the above mutations for specific species of genus, bovine. No other myostatin variance sequences from **other species** which are correlated with increased muscle mass are disclosed.

The State of prior art & Unpredictability:

McPherron et al. (PNAS, November 1997, vol. 94, pages 12457-12461) evidences that a mutation present in one species responsible for a particular phenotype is not necessarily found in other species of the same genus. **McPherron et al. demonstrates that a mutation found in a bovine species, Belgian Blue exhibiting increased muscle mass phenotype is not found in the bovine species**, Piedmontese exhibiting the same phenotype. Similarly, the mutation responsible for increased muscle mass phenotype in Piedmontese is not present in Belgian Blue.

Hence, it is clear that correlation of a genotype to a particular phenotype is highly unpredictable and requires empirical determination for each of the species. While a region of myostatin gene might be highly conserved across species, not all mutations are conserved across species. McPherron et al. clearly evidences this fact in that two species of the same genus (bovine)

exhibiting a same phenotype (increased muscle mass) comprises mutually exclusive mutation in myostatin gene.

Skill Level:

The skill level of the artisan is deemed high.

Amount of Experimentation:

One of skilled in the art, in order to practice the full scope of the invention would need to first identify mutations which are present in all species embraced by subgenus of bovine, the mutations of which are responsible for producing increased muscle mass in each of said species. As the instant specification does not give any guidance for implicating the increased muscle mass with 937-947 deletion mutation in species other than that of the Belgian Blue, one of skill in the art must conduct empirical experimentation of each of the species, the experimentation of which must consider a reasonable number of samples so as to produce a statistically significant result, the experimentation of which considers both homozygous and heterozygous mutations, amounting to an undue amount of experimentation to practice the invention commensurate in scope of the claims.

Rejections, New Grounds – Necessitated by Amendment

Claims 34 and 35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of detection for Piedmontese myostatin variant nucleotide sequence having a homozygous G1056A substitution, wherein the probe hybridizes to SEQ ID Number 8, wherein the probe is SEQ ID Number 12, does not reasonably provide enablement for the method wherein the probe hybridizes to SEQ ID Number 6, wherein the probe is SEQ ID Number 10. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

SEQ ID Number 6 is disclosed as being the mutation site for the 11 base pair deletion in exon 3 of Belgian Blue (Figure 1C and page 4, instant specification) and SEQ ID Number 10 is complementary thereto.

Thus, SEQ ID Numbers 6 and 10 cannot be employed in the method of detection in Piedmontese, for the variant nucleotide sequence having a homozygous G1056A substitution, thereby failing one of skill in the art to practice the invention fully commensurate in scope of the claims without undue experimentation.

Claim Rejections - 35 USC § 102

The rejection of claims 28-30, 36, 37, 42, and 54 under 35 U.S.C. 102(a) as being anticipated by Kambadur et al. (Genome Research September 1997, vol. 7, no. 9, pages 910-916), made in the Office Action mailed on January 31, 2006 is withdrawn in view of the Amendment received on July 5, 2006, canceling the rejected claims. With respect to the rejection of claims 25-27, 33, 40, 55, and 56 under the same heading, the rejection is withdrawn solely based on Applicants' declaration which antedates the publication date of Kambadur et al., received in the Amendment received on July 5, 2006.

The rejection of claims 28, 29, 36, 37, 42, and 54, under 35 U.S.C. 102(e) as being anticipated by Grobet et al. (U.S. Patent No. 6,103,466, issued August 15, 2000, filed July 14, 1997), made in the Office Action mailed on January 31, 2006 is withdrawn in view of the Amendment received on July 5, 2006, canceling the rejected claims. With respect to the rejection of claims 25-27, 33, 40, 55, and 56 under the same heading, the rejection is withdrawn in view of the Amendment received on July 5, 2006, amending the claims only to detection of myostatin variant nucleotide sequence having a homozygous G1056A substitution, which is not taught by Grobet et al.

Rejections, New Grounds, Necessitated by Amendment

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 66-68 are rejected under 35 U.S.C. 102(e) as being anticipated by Grobet et al. (U.S. Patent No. 6,103,466, issued August 15, 2000, filed July 14, 1997).

Grobet et al. disclose a method of detecting the presence of mutation in myostatin gene, from a subject wherein the presence of said mutation is correlated with the subject having an increased muscle mass (column 2, lines 63-65; column 2 line 66 to column 3, line 11), wherein the method comprises the steps of detecting the presence of a mutation in myostatin gene (column 3, lines 13-22).

With regard to claim 67, the method comprises the step of amplifying the nucleic acid harboring the mutation (column 3, line 18-20; column 10, lines 66-67).

With regard to claim 68, the artisans explicitly state that, "primer pairs flanking the deletion [mutation] ...were prepared." (column 10, lines 66-67).

The mutation is an 11-base pair nucleotide deletion (see Figure 2A; column 2, line 61; and column 11, lines 8-9).

The deletion of the 11-base pair is disclosed as producing a truncated protein (column 10, lines 56-60), wherein the deletion causes a frame-shift resulting in a premature stop-codon after 13 encoded amino acids.

The artisans also disclose that a probe is hybridized to the site of the mutation for detection (column 14, lines 37-38).

The subject is Belgian Blue, a species of bovine (column 4, line 58; column 11, lines 8-9; column 14, line 42).

The 11-base pair is disclosed being homozygous (column 11, lines 9-10).

The specimen is a skeletal muscle tissue (claims 10 and 11 on column 59).

Therefore, the invention as claimed is clearly anticipated by Grobet et al.

Response to Arguments:

While Applicants arguments are not drawn to the new claims, to the extent applicable, the arguments are addressed herein.

Applicants arguments are drawn to the fact that the instant application should be accorded the filing date of the parent application serial no. 08/525,596, filed on October 26, 1995, and from this accordance, the rejection should be withdrawn as antedating the reference of record (page 13, bottom paragraph).

Specifically, Applicants contend that for example, U.S. Patent No. 5,994,618 to which the instant application claims priority, is directed to myostatin knock-out transgenic animals, which have increased muscle mass as compared to a subject having a wild-type nucleic acid sequence, wherein Applicants point to example 8, as well as issued-claims 2 and 5 which provide support for methods for detecting variant myostatin in a sample, whether in one or both alleles.

It is respectfully pointed out that the claims are drawn to a method pertaining to a bovine species, and in particular Piedmontese, wherein the method further comprises the detection of a specific mutation, that is G1056A substitution in Piedmontese.

The specification of the referenced patent application does not have any written support for the method of detection pertaining to the specific species of bovine as claimed.

While knock-out transgenic animals are employed and disclosed in the above referenced patent document, the knock-out transgenic is mice (column 28, lines 31-67).

The patent document does disclose that non-human animals of the invention embraces bovine, ovine and avian animals (column 16, lines 32-34). However, the patent document does not contemplate the detection of the specific mutations in the specific bovine species so as to provide proper written support under 35 U.S.C. 112, 1st paragraph.

With Applicants' statement regarding that Applicants were the first to clone the bovine myostatin sequence which is provided in the priority applications as well as deposited in GenBank assession no. AF019620 (page 10, bottom paragraph, Response), the disclosure of the gene does not provide support for a method of detecting for a particular phenotype based on a particular mutations found therein. In addition, the support under 35 U.S.C. 112, 1st paragraph requires that the applications from which priority is claimed must provide written support and not other publications. If such were so, then no references would be applicable under prior art rejection. For the above reasons, the effective priority is properly determined and is accorded the date of November 10, 1997).

Therefore, the reference of record is prior art and the rejection is maintained.

Claim Rejections - 35 USC § 103

The rejection of claims 31, 32, 34, 35, 43-50, and 53 under 35 U.S.C. 103(a) as being unpatentable over Kambadur et al. (Genome Research September 1997, vol. 7, no. 9, pages 910-916) in view of Valent et al. (Molecular Microbiology, July 1997, vol. 25, no. 1, pages 53-64), made in the Office Action mailed on January 31, 2006 is withdrawn in view of the declaration received with the Amendment received on July 5, 2006. Specifically, Kambadur et al. is not prior art in view of the convincing evidence supplied in said declaration.

The rejection of claims 34 and 35 under 35 U.S.C. 103(a) as being unpatentable over Grobet et al. (U.S. Patent No. 6,103,466, issued August 15, 2000, filed July 14, 1997), made in the Office Action mailed on January 31, 2006 is withdrawn in view of the Amendment received on July 5, 2006, amending the claims to the detection of myostatin variant nucleotide sequence having a homozygous G1056A substitution, which is not taught by Grobet et al.

Rejection, Maintained

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 43-46 under 35 U.S.C. 103(a) as being unpatentable over Grobet et al. (U.S. Patent No. 6,103,466, issued August 15, 2000, filed July 14, 1997), made in the Office Action mailed on January 31, 2006 is maintained for the reasons of record.

Applicants' arguments presented in the Amendment received on July 5, 2006 have been fully considered but they are not found persuasive for the reasons set forth in the, "Response to Arguments," section.

Preliminarily, Applicants are advised that the instantly rejected claims require only one of the two probes which detect two different mutations. Since the mutation drawn to Belgian Blue is taught by Grobet et al., the rejection is based on this embodiment.

The Rejection:

Grobet et al. disclose a method of detecting the presence of mutation in myostatin gene, from a subject wherein the presence of said mutation is correlated with the subject having an increased muscle mass (column 2, lines 63-65; column 2 line 66 to column 3, line 11), wherein the method comprises the steps of detecting the presence of a mutation in myostatin gene (column 3, lines 13-22).

The method comprises the step of amplifying the nucleic acid harboring the mutation (column 3, line 18-20; column 10, lines 66-67).

The artisans explicitly state that, "primer pairs flanking the deletion [mutation] ...were prepared." (column 10, lines 66-67).

The mutation is an 11-base pair nucleotide deletion (see Figure 2A; column 2, line 61; and column 11, lines 8-9).

The deletion of the 11-base pair is disclosed as producing a truncated protein (column 10, lines 56-60), wherein the deletion causes a frame-shift resulting in a premature stop-codon after 13 encoded amino acids (see Figure 1C; and page 913 for its description).

The artisans also disclose that a probe hybridization to a site of the mutation is also employed for detection (column 14, lines 37-38).

The subject is Belgian Blue, a species of bovine (column 4, line 58; column 11, lines 8-9; column 14, line 42).

The 11-base pair is disclosed being homozygous (column 11, lines 9-10).

The specimen is a skeletal muscle tissue (claims 10 and 11 on column 59).

Grobet et al., do not explicitly disclose that their method employs a probe sequence which hybridizes to SEQ ID No. 6, 8, wherein said probe consists of SEQ ID No. 10 or 12.

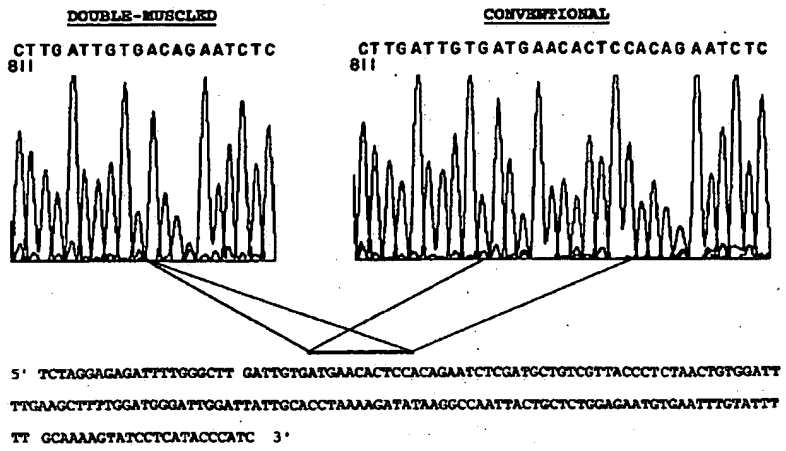
Grobet et al. do not explicitly disclose a kit comprising, in a first container, a nucleic acid hybridization probe which hybridizes to SEQ ID Numbers 6 or 8 (claim 43), wherein said nucleic acid hybridization probe is selected from SEQ ID Numbers 10 or 11 (claim 44), said kit further comprising amplification polymerase and dNTPs (claim 45), detectable means (claim 46).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to employ the nucleic acid hybridization probe of SEQ ID No. 10, which hybridizes to a nucleic acid sequence of SEQ ID No. 6, in the method of Grobet et al., thereby arriving at the claimed invention for the following reasons.

Grobet et al. state that their detection method – the step of detecting the DNA encoding an allelic protein lacking the activity – correlates that a subject has muscular hyperplasia (or increased muscle mass) (see column 3, lines 1-8).

Grobet et al. are also explicit in disclosing that this DNA encoding an allelic protein, is an 11-base pair deletion (column 4, lines 52-55).

Figure 2A of the sequence disclosed by Grobet et al. compares the location of this 11-bp deletion with respect to the wild-type sequence (see below):



Grobet et al. disclose a mutant myostatin nucleic acid sequence (SEQ ID NO: 3), which lacks the above- 11-bp deletion (see below):

```
ACA CCA AAA AGA TCT AGG AGA GAT TTT GGG CTT GAT TGT GAC AGA ATC      871
Thr Pro Lys Arg Ser Arg Arg Asp Phe Gly Leu Asp Cys Asp Arg Ile
260                 265                 270                 275


TCG ATG CTG TCG TTA CCC TCT AAC TGT GGA TTT TGAAGCTTTT              914
Ser Met Leu Ser Leu Pro Ser Asn Cys Gly Phe
                ---                 ---
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Therefore, while Grobet et al. do not explicitly disclose a probe sequence that consists of SEQ ID Number 10, which hybridizes to SEQ ID Number 6, one of ordinary skill in the art at the time the invention was made would have been clearly motivated to derive an oligonucleotide probe hybridizing to this deletion site so as to identify whether a subject is predisposed or is having increased muscle mass as a result of the disclosed mutation with a reasonable expectation of success. Given that a mutation is known, it is well-within the purview of an ordinarily skilled artisan to derive an oligonucleotide probe of the requisite length so as to detect the mutation with high specificity.

With regard to claims 43 and 44, one of ordinary skill in the art would have been motivated to package the above derived oligonucleotide probe in view of the conventionality of kits in the

analytical arts for the advantages of convenience, cost-effectiveness, matched and/or preweighed components, etc.

With regard to claims 45 and 46, Grobet et al. discloses that their method employs amplification of the nucleic acid segment comprising the mutation (column 14, lines 22-25) via PCR and that the amplified target is labeled (column 11, lines 1-3). It is well known in the art that PCR (polymerase chain reaction) employs an amplification polymerase such as Taq polymerase. Hence, it would have been obvious to one of ordinary skill in the art at the time the invention was made to also package the polymerase and labels in to the same kit for the same benefit of convenience, cost-effectiveness, matched and/or preweighed components.

The invention as claimed is *prima facie* obvious over Grobet et al.

Response to Arguments:

Applicants' argument is based on the contention that Grobet et al. would not be "prior art" if the instant application was accorded priority to the parent application serial no. 08/525,596, filed on October 26, 1995 (page 14, 2nd paragraph, Response).

It is pointed out that the priority argument has been fully addressed above, and has not been found persuasive.

Applicants are invited to point specific pages and lines of the application in question, for the support of detecting the particular mutation in Belgian Blue.

Rejections, New Ground – Necessitated by Amendment

Claims 47-50, 69 and 70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grobet et al. (U.S. Patent No. 6,103,466, issued August 15, 2000, filed July 14, 1997) in view of Valent et al. (Molecular Microbiology, July 1997, vol. 25, no. 1, pages 53-64).

Grobet et al. disclose a method of detecting the presence of mutation in myostatin gene, from a subject wherein the presence of said mutation is correlated with the subject having an increased muscle mass (column 2, lines 63-65; column 2 line 66 to column 3, line 11), wherein the method comprises the steps of detecting the presence of a mutation in myostatin gene (column 3, lines 13-22).

The method comprises the step of amplifying the nucleic acid harboring the mutation (column 3, line 18-20; column 10, lines 66-67).

The artisans explicitly state that, "primer pairs flanking the deletion [mutation] ...were prepared." (column 10, lines 66-67).

The mutation is an 11-base pair nucleotide deletion (see Figure 2A; column 2, line 61; and column 11, lines 8-9).

The deletion of the 11-base pair is disclosed as producing a truncated protein (column 10, lines 56-60), wherein the deletion causes a frame-shift resulting in a premature stop-codon after 13 encoded amino acids (see Figure 1C; and page 913 for its description).

The artisans also disclose that a probe hybridization to a site of the mutation is also employed for detection (column 14, lines 37-38).

The subject is Belgian Blue, a species of bovine (column 4, line 58; column 11, lines 8-9; column 14, line 42).

The 11-base pair is disclosed being homozygous (column 11, lines 9-10).

The specimen is a skeletal muscle tissue (claims 10 and 11 on column 59).

Grobet et al., do not explicitly disclose that their method employs a flanking primer sequence which hybridizes to SEQ ID No. 1 and 2, wherein said primer sequences consists of SEQ ID No. 3 and 4.

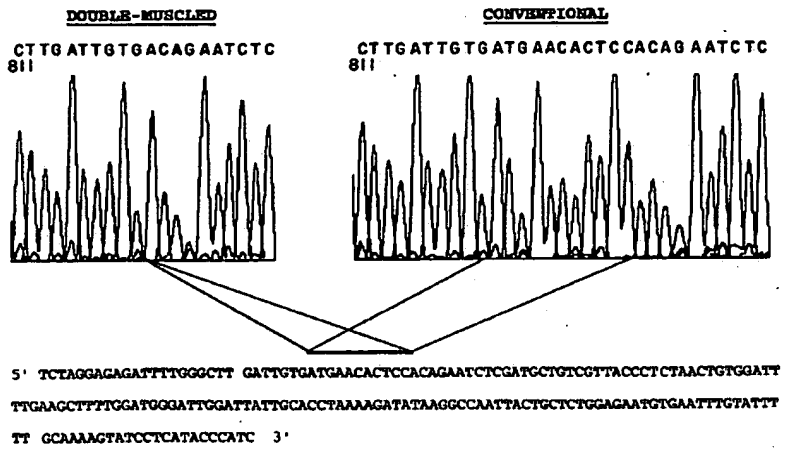
Valent et al. disclose a well known method amplifying a target nucleic acid via use of a pair of primers flanking the target nucleic acid, wherein said pair of primers comprise a BamHI recognition site at their 5' ends, for the purpose of cloning and sequencing reaction (page 62, 1st column, see 2nd paragraph). In particular, Valent et al. employ a primer comprising the following sequence, 5'-CGCGGATCC-target sequence-3' (BamHI recognition underlined).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to employ the primers of SEQ ID Numbers 3 and 4, which hybridizes to a nucleic acid sequence of SEQ ID Numbers 1 and 2 (respectively), in the method of Grobet et al. and combine the teachings of Valet et al., thereby arriving at the claimed invention for the following reasons.

Grobet et al. state that their detection method – the step of detecting the DNA encoding an allelic protein lacking the activity – correlates that a subject has muscular hyperplasia (or increased muscle mass) (see column 3, lines 1-8).

Grobet et al. are also explicit in disclosing that this DNA encoding an allelic protein, is an 11-base pair deletion (column 4, lines 52-55).

Figure 2A of the sequence disclosed by Grobet et al. compares the location of this 11-bp deletion with respect to the wild-type sequence (see below):



Grobet et al. disclose a mutant myostatin nucleic acid sequence (SEQ ID NO: 3), which lacks the above- 11-bp deletion (see below):

```
ACA CCA AAA AGA TCT AGG AGA GAT TTT GGG CTT GAT TGT GAC AGA ATC      871
Thr Pro Lys Arg Ser Arg Arg Asp Phe Gly Leu Asp Cys Asp Arg Ile
260                 265                 270                 275


TCG ATG CTG TCG TTA CCC TCT AAC TGT GGA TTT TGAAGCTTTT              914
Ser Met Leu Ser Leu Pro Ser Asn Cys Gly Phe
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Therefore, while Grobet et al. do not explicitly disclose a primer pair that flanks the 11 base pair deletions, one of ordinary skill in the art at the time the invention was made would have been clearly motivated to derive appropriate flanking oligonucleotide primers flanking said deletion site so as to identify whether a subject is predisposed or is having increased muscle mass as a result of the disclosed mutation with a reasonable expectation of success. Given that a mutation is known and the gene is known, it is well-within the purview of an ordinarily skilled artisan to derive any pair of oligonucleotide primers flanking the mutation, so as to detect the mutation with high specificity.

With regard to the combination of the teachings of Grobet et al. with the teachings of Grobet et al., this is, employing the restriction enzyme recognition sequence on the 5' end of the primers, such practice of adding restriction recognition site into the primers for the purpose of

cloning and sequencing the amplified sequence is well known and established as evidenced by Valent et al. Hence, one of ordinary skill in the art at the time the invention was made would have had a clear expectation of success at combining the teachings of Grobet et al. and Valent et al., thereby arriving at the invention as claimed.

With regard to the packaging the contents of the element taught by the artisan in to a kit, (as in claims 47-50), one of ordinary skill in the art would have been motivated to package the above derived oligonucleotide probe in view of the conventionality of kits in the analytical arts for the advantages of convenience, cost-effectiveness, matched and/or preweighed components, etc.

For the above reasons, the invention as claimed is *prima facie* obvious over the cited references.

Double Patenting

Claim duplicate warning between claim 50 and 53, made in the Office Action mailed on January 31, 2006 is withdrawn in view of the Amendment received on July 5, 2006, canceling claim 53.

Conclusion

No claims are allowed.

It appears that Applicants have not filed a terminal disclaimer over U.S. Patent No. 6,673,534, as suggested in the previous Office Action. Applicants are encouraged to file a Terminal Disclaimer so as to facilitate examination process.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner is on flex-time schedule and can best be reached from 8:30 a.m. to 4:30 p.m. The Examiner can also be reached via e-mail to Young.Kim@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary Benzion, can be reached at (571) 272-0782.

Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED,

so as to avoid the processing of duplicate papers in the Office. All official documents must be sent to the Official Tech Center Fax number: (571) 273-8300. For Unofficial documents, faxes can be sent directly to the Examiner at (571) 273-0785. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Young J. Kim
Patent Examiner
Art Unit 1637
9/12/2006

YOUNG J. KIM
PRIMARY EXAMINER

yjk